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Critical Power and Respiratory Compensation Point Are Not Equivalent in Patients with COPD

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ABSTRACT

TILLER, N. B., J. PORSZASZ, R. CASABURI, H. B. ROSSITER, and C. FERGUSON. Critical Power and Respiratory Compensation Point Are Not Equivalent in Patients with COPD. *Med. Sci. Sports Exerc.*, Vol. 55, No. 6, pp. 1097–1104, 2023. **Introduction:** Several studies report that pulmonary oxygen uptake ($\dot{V}O_2$) at the respiratory compensation point (RCP) is equivalent to the $\dot{V}O_2$ at critical power (CP), suggesting that the variables can be used interchangeably to demarcate the threshold between heavy and severe intensity domains. However, if RCP is a valid surrogate for CP, their values should correspond even when assessed in patients with chronic obstructive pulmonary disease (COPD) in whom the "normal" mechanisms linking CP and RCP are impeded. The aim of this study was to compare $\dot{V}O_2$ at CP with $\dot{V}O_2$ at RCP in patients with COPD. **Methods:** Twenty-two COPD patients (14 male/8 female; forced expiratory volume in 1 s, 46% ± 17% pred) performed ramp-incremental cycle ergometry to intolerance (5–10 W·min^{-1}) for the determination of gas exchange threshold (GET) and RCP. CP was calculated from the asymptote of the hyperbolic power–duration relationship from 3–5 constant-power exercise tests to intolerance. CP was validated with a 20-min constant-power ride. **Results:** GET was identified in 20 of 22 patients at a $\dot{V}O_2$ of 0.93 ± 0.18 L·min^{-1} (75% ± 13% $\dot{V}O_{2peak}$), whereas RCP was identified in just 3 of 22 patients at a $\dot{V}O_2$ of 1.40 ± 0.39 L·min^{-1} (85% ± 2% $\dot{V}O_{2peak}$). All patients completed constant-power trials with no difference in peak physiological responses relative to ramp-incremental exercise ($P > 0.05$). CP was 46 ± 22 W, which elicited a $\dot{V}O_2$ of 1.04 ± 0.29 L·min^{-1} (90% ± 9% $\dot{V}O_{2peak}$) during the validation ride. The difference in $\dot{V}O_2$ at 15 and 20 min of the validation ride was 0.00 ± 0.04 L, which was not different from a hypothesized mean of 0 ($P = 0.856$), thereby indicating a $\dot{V}O_2$ steady state. **Conclusions:** In COPD patients, who present with cardiopulmonary and/or respiratory-mechanical dysfunction, CP can be determined in the absence of RCP. Accordingly, CP and RCP are not equivalent in this group. **Key Words:** EXERCISE, EXERCISE LIMITATION, LUNG FUNCTION, LUNG DISEASE

The relationship between power output and time to the limit of tolerance (T_{lim}) during non–steady-state exercise is characterized by two variables. First is critical power (CP)—the asymptote of the hyperbolic power–T_{lim} (P–T_{lim}) relationship—which demarcates the boundary between the heavy- and severe-intensity domain (1). Second is W'—the curvature constant of the P–T_{lim} relationship—which characterizes the finite work that can be accomplished above CP before intolerance (1–4). CP is associated with endurance performance, is sensitive to endurance training (5–8), and is influenced by conditions that affect O_2 transport and/or utilization (such as hypoxia/hyperoxia (9–11) and cardiopulmonary disease (12,13)).

The P–T_{lim} relationship provides a framework with which to explore the mechanistic basis of exercise intolerance and fatigue (1). However, the gold-standard protocol for characterizing the P–T_{lim} relationship and thus obtaining estimates of CP and W' is both time-consuming and highly strenuous for the participant—requiring at least three exercise tests, performed at a severe intensity, to the limit of tolerance. As such, CP is not routinely measured during laboratory-based exercise testing. As possible alternatives to the gold-standard approach, researchers have studied a 3-min "all-out" test (8,14), a combined "ramp-sprint" protocol (15), and whether the deoxyhemoglobin breakpoint or the respiratory compensation point (RCP) during ramp-incremental exercise are valid surrogates for CP (16–20).

The scientific validity of RCP as a CP surrogate is an ongoing point of contention. In healthy adults, some studies show that CP and RCP occur at a similar rate of pulmonary oxygen uptake ($\dot{V}O_2$) (19,21) and power output (21,22), suggesting that the thresholds may be interchangeable. By contrast, Broxterman and colleagues (18) concluded that treadmill speed and $\dot{V}O_2$ at critical speed and RCP were merely coincident (not equivalent) owing to the high degree of within-subject variability between measures. Data from Leo and colleagues (20) showed that power output at RCP, identified during ramp-incremental exercise, had

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poor agreement with CP, and others suggest that CP and RCP should not be used interchangeably because they respond differently to chronic exercise training (23). Lastly, because of the confounding effects of the kinetic dissociation between $\dot{V}O_2$ and power output during non–steady-state exercise, several studies are equivocal on whether an association between CP/speed and RCP exists (18,24). Accordingly, there is no consensus on the equivalence of $\dot{V}O_2$ and/or power output at CP and RCP.

To date, the equivalence of CP and RCP has only been explored in healthy or athletic populations with normal cardiopulmonary function. However, the validity of the "equivalence hypothesis" depends on several assumptions, the most pertinent being that the signaling pathways connecting metabolic acidosis (originating in active muscles) and respiratory compensation (achieved by the ventilatory system) are unaffected by environment or pathophysiology.

Chronic obstructive pulmonary disease (COPD) is a progressive disorder underpinned by airway inflammation and remodeling, diminished airway caliber, and/or pulmonary emphysema (25). Patients with COPD exhibit deranged breathing mechanics characterized by expiratory flow limitation and dynamic hyperinflation, which predispose to dyspnea and exercise intolerance (26). Many COPD patients also have altered chemoreceptor sensitivity that affects the ventilatory response to exercise (27). Based on the pathophysiology, it may be that few COPD patients have the respiratory-mechanical function and/or the signaling pathways necessary to exhibit respiratory compensation during incremental exercise. However, to our knowledge, this has not been empirically studied. Data from patients with respiratory dysregulation, in whom the "normal" physiological cascade that connects CP and RCP is impeded, would provide a decisive answer as to the true "coincidence or equivalence" between these two measures. This exploratory study therefore assessed the prevalence with which COPD patients exhibited respiratory compensation during ramp-incremental exercise and compared $\dot{V}O_2$ at the RCP to that measured at CP.

METHODS

Experimental Overview

This study used previously published ramp-incremental and constant-power exercise data from COPD patients (28,29) to address a novel research question. Participants attended the laboratory on four occasions (separated by >48 h) to complete the experimental protocol. At the first visit, they provided written, informed consent; had their vital signs and resting electrocardiogram assessed; and performed a prebronchodilator and postbronchodilator pulmonary function test. Participants also completed a ramp-incremental exercise test on a cycle ergometer for the determination of gas exchange threshold (GET), RCP, and $\dot{V}O_{2peak}$. Visits 2 and 3 each comprised two constant-power exercise tests (separated by >2 h) to the limit of tolerance for the determination of CP and W'. During these visits, the test with the lowest power output was performed first to minimize carryover effects (30). At the final visit, participants performed a 20-min constant-power "validation" trial at their calculated CP to assess for a physiological steady state.

Participants

Participants were current or former smokers with COPD. Inclusion criteria were postbronchodilator forced expiratory volume in 1 s (FEV_1) <80% predicted, age 40–80 yr (inclusive), no exacerbations within 4 wk, and no other known risk factors or comorbidities. The final sample comprised 22 patients in whom all required data were available (14 male/8 female; see Table 1 for patient characteristics and pulmonary function). The study was approved by the institutional review board at the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center and was conducted in accordance with the Declaration of Helsinki except for principle 35 (public trial registration). All participants abstained from intense exercise for 48 h, alcohol and caffeine for 12 h, and food for 3 h before each visit.

Pulmonary Function Tests

Forced vital capacity (FVC) and FEV_1 were assessed via spirometry (Vmax 229; VIASYS SensorMedics, Yorba Linda, CA). Values were expressed as percentages of predicted norms according to the National Health and Nutrition Examination Survey III standards (31). Maximum voluntary ventilation (MVV) was estimated as $FEV_1 \times 40$ (32). Pulmonary function tests were carried out in accordance with recommended standards (33).

Exercise Tests

Exercise was performed on an electrically braked cycle ergometer (Ergoline 800; SensorMedics) at a predetermined cadence of 60 rpm (actual cadence, 60 ± 3 rpm). Exercise continued to the limit of tolerance, determined as the point at which the patient was unable to maintain a crank cadence >50 rpm despite verbal encouragement. The constant-power tests were also terminated if the patient exceeded the predetermined exercise duration of 20 min. Continuous breath-by-breath measures of pulmonary gas exchange ($\dot{V}O_2$, rate of pulmonary carbon dioxide output ($\dot{V}CO_2$)) and minute ventilation ($\dot{V}_E$) were made via metabolic cart (Vmax Spectra; SensorMedics), arterial O_2

TABLE 1. Patient characteristics and postbronchodilator pulmonary function.

	Overall (n = 22)
Demographics	
Male/Female (n)	14/8
GOLD status = 1, 2, 3, 4 (n)	0, 11, 7, 4
Age (yr)	63 ± 9
Mass (kg)	79.4 ± 13.7
Stature (cm)	170.0 ± 7.0
Pulmonary function	
FVC (L)	3.17 ± 1.03
FEV_1 (L)	1.30 ± 0.50
FEV_1 (%pred)	46.8 ± 17.7
FEV_1/FVC (%)	41.8 ± 12.5
MVV ($L \cdot min^{-1}$)	51.9 ± 20.1

Mean ± SD. Spirometry reference values taken from the National Health and Nutrition Examination Survey III study (31).
GOLD, Global Initiative for Chronic Obstructive Lung Disease.

saturation via pulse oximetry, and heart rate (f_C) via 12-lead electrocardiogram.

Ramp-incremental test. Ramp-incremental exercise was used to determine GET, RCP, and $\dot{V}O_{2peak}$, and to derive work rates for the constant power tests. After 3-min seated rest, exercise began with 3-min unloaded cycling (0 W) after which the power output increased continuously by 5 W·min^{-1} (for patients with FEV_1 ≤1.0 L) or 10 W·min^{-1} (for patients with FEV_1 >1.0 L). The breath-by-breath data were exported from the Vmax system as 10-s bin-averaged means, smoothed using a 3-point rolling average, and plotted in a nine-panel report (Sigma Plot version 13.0; Systat Software Inc., Chicago, IL). Two reviewers independently identified and verified GET and RCP using standard criteria (34). Specifically, GET was identified from the inflection point in the V-slope relationship and corroborated by inspection of the $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ responses; RCP was identified using the $\dot{V}_E$ versus $\dot{V}CO_2$ relationship and corroborated by inspection of the $\dot{V}_E/\dot{V}CO_2$ and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) responses. Peak variables were calculated as the highest 30-s average.

Constant-power tests. Constant power tests were used to determine CP and W' and to verify CP estimation. After 3-min seated rest, exercise began with 3-min unloaded cycling (0 W) after which power output increased to a predetermined level and was maintained throughout the test. Power output for the four tests was calculated to elicit an even T_{lim} distribution spanning ~2–20 min, and determined as follows: power output for test 1 was equivalent to maximal power output (W_{max}) achieved during the ramp-incremental test; power output for test 2 was between 110% and 120% W_{max}; power output for test 3 was 80% W_{max}; and power output for test 4 was calculated to elicit a T_{lim} of 6–7 min based on mathematical interpolation from the first three constant-power tests. Power output and the corresponding T_{lim} for each test were used to characterize the P–T_{lim} relationship. CP (to the nearest 5 W) was calculated as the y-intercept of the regression line of power versus the inverse of endurance time ($1/T_{lim}$); W' was calculated from the slope of the linearized expression of the hyperbolic P–T_{lim} relationship ($P = [W'/(1/T_{lim})] + CP$) (4,35).

CP validation. After CP and W' had been determined, a subset of participants (n = 18) completed a validation trial during which they exercised for 20 min at the estimated CP. The difference in $\dot{V}O_2$ at 15 and 20 min was calculated to assess for a physiological steady state.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics v24 (IBM; Chicago, IL). All physiological measures ($\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio (RER), $\dot{V}_E$, $\dot{V}_E$/MVV, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}CO_2$, and f_C) were normally distributed according to Shapiro–Wilk tests. Physiological responses to ramp-incremental exercise and the constant-power trials that characterized the P–T_{lim} relationship were compared using one-way repeated-measures ANOVA with Greenhouse–Geisser adjustment if data were nonspherical. A statistically significant ANOVA was followed by pairwise comparisons using a Tukey-adjusted P value. For the CP validation trial, the mean difference in $\dot{V}O_2$ at 15 and 20 min was illustrated in a Bland–Altmann plot and compared with a hypothesized mean of 0 using a one-sample t-test. The independent relationships between $\dot{V}O_2$ at GET and CP expressed as a fraction of $\dot{V}O_{2peak}$ were assessed using Pearson's correlation coefficient. The magnitude of the difference between means (effect size) was assessed using Cohen's d (0.2, small; 0.5, medium; 0.8, large) (36). Data are presented as mean ± SD, and α level was specified *a priori* as 0.05.

RESULTS

Pulmonary function tests (postbronchodilator). Patients exhibited a moderate-to-very severe obstructive pattern (Table 1) and were classified as Global Initiative for Chronic Obstructive Lung Disease (37) spirometry stages 2 (n = 11), 3 (n = 7), and 4 (n = 4).

Ramp incremental test. Peak physiological responses to the ramp-incremental test are shown in Table 2, and responses at GET and RCP are shown in Table 3. Individual plots of the $\dot{V}_E$–$\dot{V}CO_2$ relationship during ramp-incremental exercise are shown in Figure 1. All patients completed the ramp-incremental test, achieving a $\dot{V}O_{2peak}$ of 1.22 ± 0.37 L·min^{-1}. At exercise intolerance, RER was 1.04 ± 0.12, $\dot{V}_E$ was 86% ± 17% MVV, and f_C was 74% ± 13% age-predicted maximum (38). GET was identified in 20 of 22 patients at a $\dot{V}O_2$ of 0.93 ± 0.18 L·min^{-1} (75% ± 13% $\dot{V}O_{2peak}$). RCP was identified in just 3 of 22 patients (Fig. 1) at a $\dot{V}O_2$ of 1.40 ± 0.39 L·min^{-1} (85% ± 2% $\dot{V}O_{2peak}$), $\dot{V}_E$ of 51.0 ± 17.1 L·min^{-1}, and power output of 84 ± 29 W.

Constant-power tests. Peak physiological responses to the constant-power tests are shown in Table 2, and responses at CP are shown in Table 3. All patients completed the constant-power trials, and the T_{lim} relationship among tests was

TABLE 2. Peak physiological responses to ramp-incremental and four constant-power exercise tests (ordered lowest to highest power output).

	Ramp	Constant-Power 1 (n = 22)	Constant-Power 2 (n = 22)	Constant-Power 3 v	Constant-Power 4 (n = 17)	P
Power output (W)	73 ± 28	55 ± 24	65 ± 28	78 ± 35	79 ± 29	0.038
$\dot{V}O_2$ (L·min^{-1})	1.22 ± 0.37	1.26 ± 0.35	1.26 ± 0.39	1.27 ± 0.37	1.22 ± 0.33	0.986
$\dot{V}CO_2$ (L·min^{-1})	1.30 ± 0.48	1.30 ± 0.45	1.38 ± 0.52	1.42 ± 0.52	1.29 ± 0.45	0.855
RER	1.04 ± 0.12	1.01 ± 0.11	1.07 ± 0.12	1.10 ± 0.14	1.04 ± 0.13	0.186
$\dot{V}_E$ (L·min^{-1})	44.1 ± 17.7	45.1 ± 18.0	46.2 ± 18.5	46.0 ± 18.3	43.5 ± 17.3	0.983
$\dot{V}_E$ (%MVV)	86 ± 17	88.3 ± 18.5	90.4 ± 17.9	89.4 ± 15.2	86.0 ± 17.6	0.861
$\dot{V}_E/\dot{V}CO_2$	34.2 ± 5.2	34.7 ± 5.4	33.9 ± 6.2	32.7 ± 6.1	33.8 ± 5.2	0.819
$P_{ET}CO_2$ (mm Hg)	38.2 ± 7.6	37.2 ± 8.1	38.4 ± 8.0	39.9 ± 7.5	39.1 ± 6.3	0.800
f_C (bpm)	121 ± 23	124 ± 17	123 ± 20	118 ± 16	116 ± 16	0.659
f_C (%f_{Cmax})[a]	74 ± 13	75 ± 10	75 ± 11	72 ± 9	70 ± 9	0.523

Mean ± SD, n = 22. P = ANOVA result.
[a]Age-predicted f_{Cmax} derived using 208 – (0.7 × age) (38).

TABLE 3. Physiological responses at GET (n = 20), CP (n = 18), RCP (n = 3), and $\dot{V}O_{2peak}$ (n = 22).

	Ramp-Incremental Exercise			Validation Trial
	GET (n = 20)	RCP (n = 3)	$\dot{V}O_{2peak}$ (n = 22)	CP (n = 18)
$\dot{V}O_2$ (L·min^{-1})	0.93 ± 0.18	1.40 ± 0.39	1.22 ± 0.37	1.04 ± 0.29
$\dot{V}O_2$ (%$\dot{V}O_{2peak}$)	75 ± 13	85 ± 2	100 ± 0	90 ± 9
$\dot{V}CO_2$ (L·min^{-1})	0.84 ± 0.18	1.49 ± 0.45	1.30 ± 0.48	1.00 ± 0.31
RER	0.90 ± 0.05	1.06 ± 0.05	1.04 ± 0.12	0.95 ± 0.05
$\dot{V}_E$ (L·min^{-1})	30.3 ± 6.6	51.0 ± 17.1	44.1 ± 17.7	36.6 ± 12.8
$\dot{V}_E$ (%MVV)	54 ± 25	81 ± 19	86 ± 17	78 ± 17
$\dot{V}_E/\dot{V}CO_2$	36.1 ± 4.0	34.3 ± 4.7	34.2 ± 5.2	36.7 ± 5.7
f_C (bpm)	100 ± 17	116 ± 5	121 ± 23	117 ± 20
f_C (%f_{Cmax})[a]	61 ± 10	71 ± 8	74 ± 13	72 ± 12

Mean ± SD. GET, RCP, and $\dot{V}O_{2peak}$ determined from ramp-incremental exercise; CP determined from 20-min CP validation trial.
[a]Age-predicted f_{Cmax} derived using 208 – (0.7 × age) (38).

characterized by a hyperbolic function. The mean CP and W' were 46 ± 22 W and 6064 ± 2901 J, respectively. Modeling the relationship with $1/T_{lim}$ as the independent variable did not significantly alter CP (45 ± 22 W, P = 0.901) or W' (6263 ± 2926 J, P = 0.822). Ramp-incremental and constant-power data for two patients, one with and one without an identifiable RCP, are shown in Figure 2. One-way repeated-measures ANOVA was used to compare peak physiological responses among ramp-incremental and each of the constant-power trials that characterized the P–T_{lim} relationship. There was no difference in peak $\dot{V}O_2$ (F[4,105] = 0.09, P = 0.986), indicating that maximal capacities were attained in all trials. Similarly, there was no difference with respect to $\dot{V}CO_2$ (F [4,105) = 0.33, P = 0.855), RER (F [4,105] = 1.58, P = 0.186), $\dot{V}_E$ (F [4,105] = 0.10, P = 0.983), $\dot{V}_E$/MVV (F [4,105] = 0.32, P = 0.861), $\dot{V}_E/\dot{V}CO_2$ (F [4,105] = 0.39, P = 0.819), $P_{ET}CO_2$ (F [4,105] = 0.41, P = 0.800), f_C (F [4,105] = 0.61, P = 0.659), or f_C%f_{Cmax} (age-predicted) (F [4,105] = 0.81, P = 0.523; Table 2).

Eighteen of 22 patients completed a 20-min ride at CP. Oxygen uptake at 15 and 20 min was 1.04 ± 0.28 and 1.04 ± 0.29 L·min^{-1}, respectively. The mean difference between time points was 0.00 ± 0.04 L·min^{-1}, which was not different from a hypothesized mean of 0 (P = 0.856, d = 0.04; Fig. 3). This steady-state (submaximal) $\dot{V}O_2$ helped corroborate the CP estimate.

Comparison of thresholds. The associations of $\dot{V}O_2$ at GET with ramp-incremental $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at CP with ramp-incremental $\dot{V}O_{2peak}$ are shown in Figure 4. Peak oxygen uptake during ramp-incremental exercise was strongly correlated with $\dot{V}O_2$ at GET (r^2 = 0.507, P < 0.001) and modestly correlated with $\dot{V}O_2$ at CP (r^2 = 0.340, P = 0.011). Although, on average, $\dot{V}O_2$ at GET was less than $\dot{V}O_2$ at CP (P < 0.001, d = 1.32), the difference between these thresholds (the $\dot{V}O_2$ range of the heavy-intensity domain, or "H space") decreased congruent with $\dot{V}O_{2peak}$. CP was identified in all patients, but RCP was identified in just three patients. In those three, $\dot{V}O_2$ at CP was 1.39 ± 0.23 L·min^{-1} (86% ± 11% $\dot{V}O_{2peak}$), and that at RCP was 1.40 ± 0.39 L·min^{-1} (85% ± 2%$\dot{V}O_{2peak}$; percentage discrepancy due to rounding artifact).

DISCUSSION

This study assessed the prevalence with which COPD patients exhibited RCP during ramp-incremental exercise and compared $\dot{V}O_2$ at the RCP to $\dot{V}O_2$ at CP. We were able to determine CP from the P–T_{lim} relationship in all COPD patients and corroborate the attainment of a steady-state $\dot{V}O_2$ during a 20-min ride at CP. Nevertheless, only 3 of 22 patients (14%) exhibited steepening of the $\dot{V}_E$–$\dot{V}CO_2$ slope, increased $\dot{V}_E/\dot{V}CO_2$ ratio, and/or systematically decreased $P_{ET}CO_2$ that is consistent with respiratory compensation (34). These data confirm that any equivalence between CP and RCP in previous literature results from the sequential expression of disparate physiological mechanisms that are dissociated in patients with cardiopulmonary and/or respiratory-mechanical dysfunction. This fundamentally undermines the validity of RCP as a surrogate for CP.

Technical considerations. Studies that show no equivalence between CP and RCP have been criticized for failing to validate that the calculated CP reflected the highest power output at which a steady state could be attained such that exercise was being performed using wholly oxidative metabolism (39,40). For instance, $\dot{V}O_2$ at CP was incorrectly derived from the $\dot{V}O_2$–power output relationship elicited by ramp-incremental exercise (18,23), thereby underestimating the $\dot{V}O_2$ associated with a given power output. To determine CP, we established the P–T_{lim} relationship for each patient after 3–5 constant-power exercise tests. To corroborate CP, our patients performed a 20-min constant-power trial during which we observed a steady-state $\dot{V}O_2$—that is, the mean difference between $\dot{V}O_2$ at 15 and 20 min was 0.00 ± 0.04 L·min^{-1}, which was not different from a hypothesized mean of 0 (P = 0.856, d = 0.04; Fig. 3). Although this confirms that we did not overestimate CP, we cannot say with absolute certainty that our estimated CP was the highest steady-state power (i.e., that it was not underestimated). Nevertheless, of the 3–5 constant-power trials used in the characterization of the P–T_{lim} relationship (and performed to intolerance), the test with the lowest power output was, on average, only 9 ± 8 W above the estimated CP. In addition, the power accuracy of our electrically braked cycle ergometer is ±5 W. We are therefore confident that the calculated CP was a close approximation of the highest steady-state power output.

Our data also highlight that the characteristically low $\dot{V}O_{2peak}$ of COPD patients reduces the available $\dot{V}O_2$ and power output range within each intensity domain (Fig. 4). Indeed, when $\dot{V}O_{2peak}$ is less than 10 mL·min^{-1}·kg^{-1}, it becomes difficult to differentiate between $\dot{V}O_2$ at GET, CP, and $\dot{V}O_{2peak}$. These data—the first presentation of such in the literature—contribute to our understanding of why small changes in power output can have such profound effects on exercise tolerance in COPD, particularly in patients with very low $\dot{V}O_{2peak}$.

CP and RCP. There is extensive literature on the relative proximity of CP to various metabolic/ventilatory thresholds (for a review, see (40)). Although several studies show that CP (from "all-out" or constant-power exercise) and RCP (from ramp-incremental exercise) occur at equivalent power outputs in healthy subjects (21,22), the validity of this finding is dependent on (at least) three important assumptions: i) that CP is a power output; ii) that the kinetic dissociation between power output and physiological responses to ramp-incremental exercise (e.g., $\dot{V}O_2$, $\dot{V}_E$, $\dot{V}CO_2$) does not significantly influence the

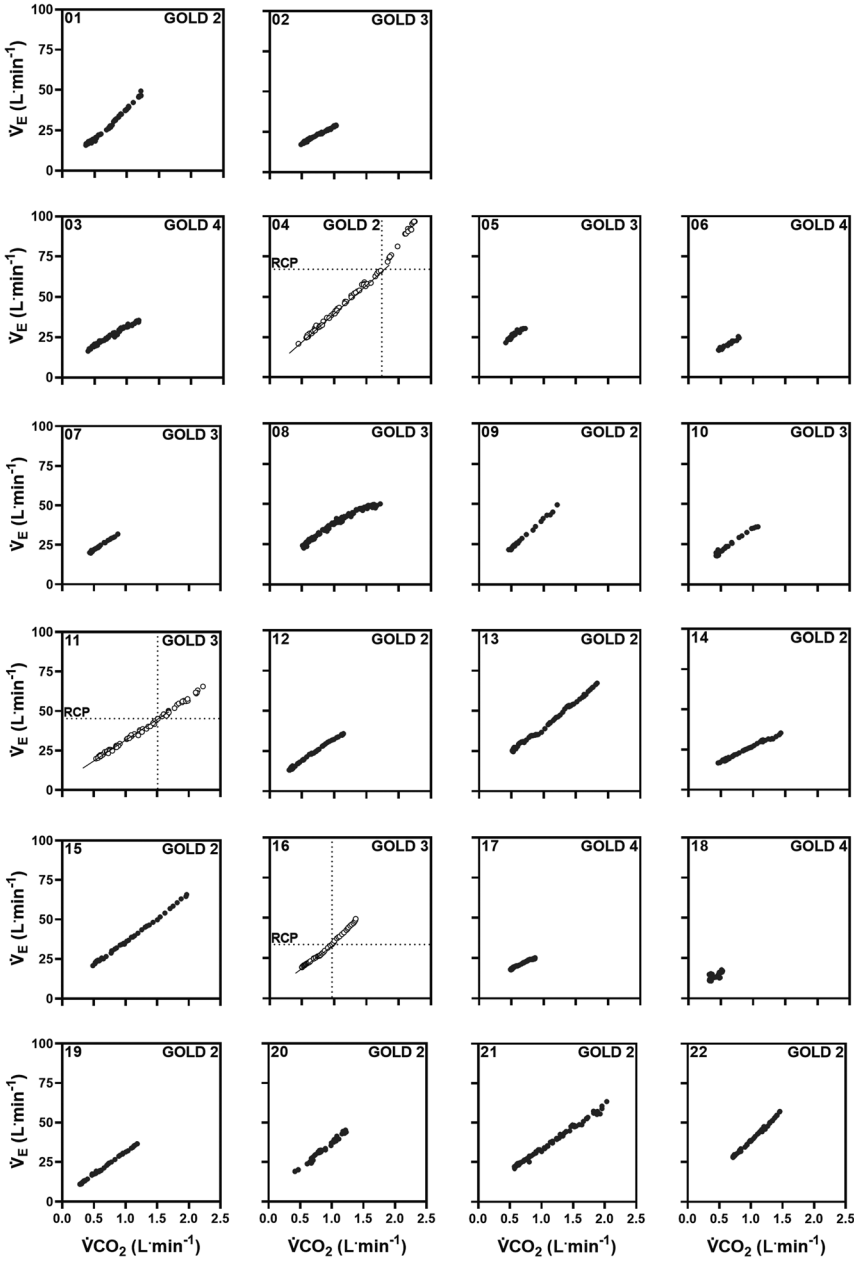
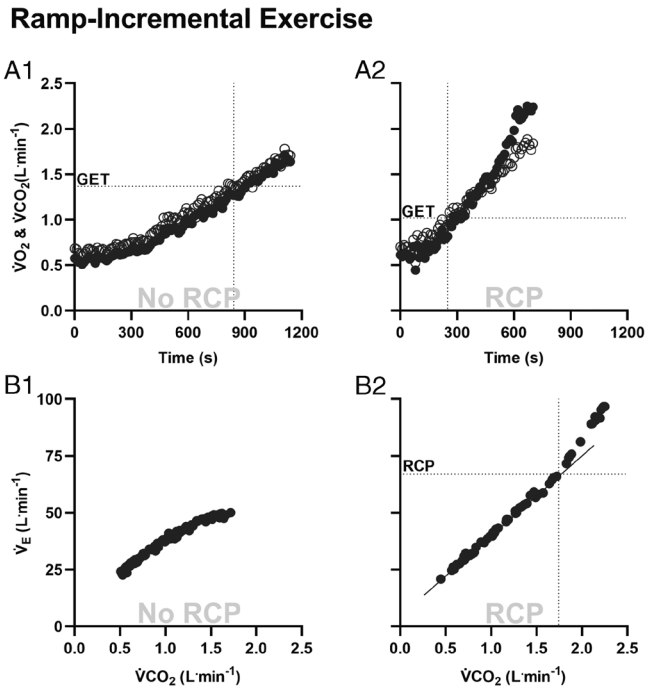


FIGURE 1—Individual participant $\dot{V}_E$–$\dot{V}CO_2$ responses during ramp-incremental exercise. Only 3 of 22 patients (patients 4, 11, and 16) had an identifiable RCP.

association between CP and RCP; and iii) that the signaling pathways connecting metabolic acidosis (originating in active muscles) and respiratory compensation (achieved by the ventilatory system) are unaffected by environment or pathophysiology.

Regarding the first assumption, although CP is typically measured in the power domain (e.g., quantified as watts during cycle ergometry), the absolute value recorded by the ergometer's external sensor assumes that the internal (unmeasured) power—that in the form of instrumental friction or work required to move the locomotor muscles against the force of gravity—remains constant. Indeed, Barker et al. (41) showed that external power on the flywheel was influenced by pedal cadence, but that total power measured as $\dot{V}O_2$ was independent of cadence and remained constant. In this sense, it may be more appropriate to consider CP in terms of $\dot{V}O_2$, which, through knowledge of exercise economy, can be coupled with a range of external powers. On examination, CP is actually an emergent property of muscle metabolism, depending partly on activity of oxidative enzymes, describing the highest rate of ATP utilization that can be met with intramuscular metabolic stability (39,40). Nevertheless, internal work can only be assumed to be constant under controlled laboratory conditions wherein factors like pedal cadence, which would normally confound the P–T_{lim} model, can be tightly controlled. It may be reasonable therefore to explore an equivalence between power output at CP and RCP in laboratory studies when the other two assumptions are met.

The second assumption is that the relationship between CP and RCP is not influenced by the kinetic dissociation between



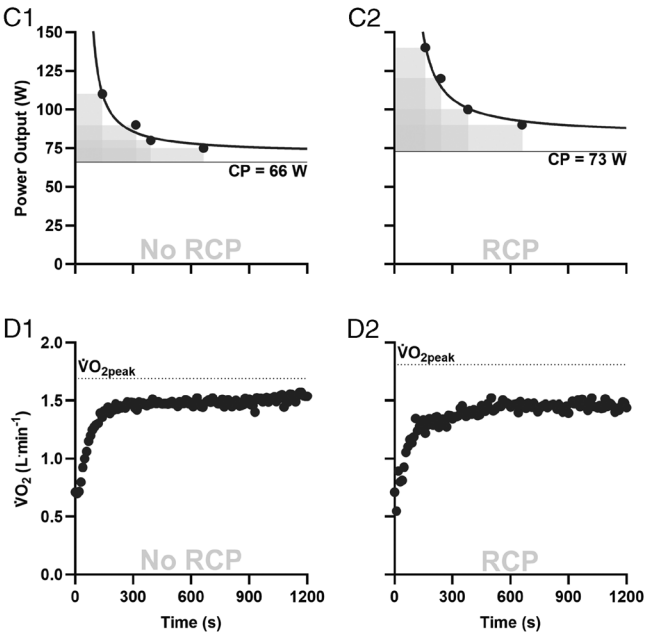


FIGURE 2—Representative data (n = 2) from ramp-incremental and constant-power exercise. Panels on the left show data from a patient without an identifiable RCP, and panels on the right show data from a patient with an identifiable RCP. Panels A1 and A2 illustrate the $\dot{V}O_2$–$\dot{V}CO_2$ relationship during ramp-incremental exercise on which the identified GET has been overlayed. Panels B1 and B2 illustrate RCP from the $\dot{V}_E$–$\dot{V}CO_2$ relationship during ramp-incremental exercise. Panels C1 and C2 illustrate the hyperbolic P–T_{lim} relationship and the calculated CP (66 vs 73 W) during constant-power exercise. Panels D1 and D2 illustrate $\dot{V}O_2$ from a 20-min CP ride during which $\dot{V}O_2$ reached a steady state.

power output and physiological responses to ramp-incremental exercise. RCP is determined during ramp-incremental exercise as an increase in the slope of the $\dot{V}_E$–$\dot{V}CO_2$ relationship,

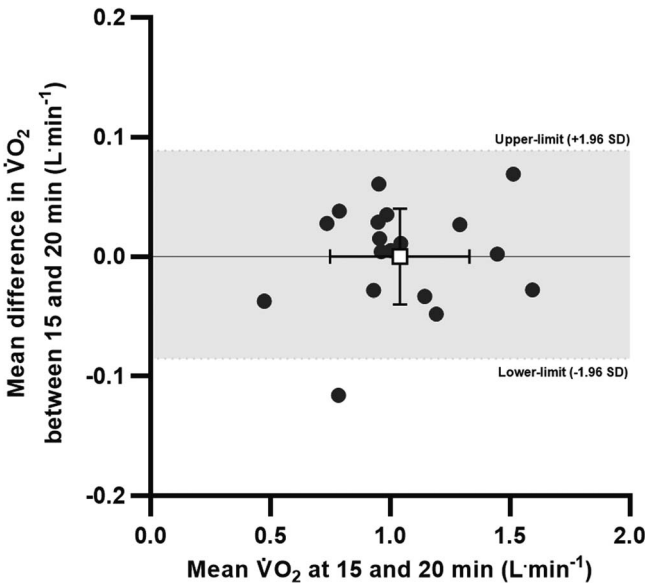


FIGURE 3—Bland–Altman plot showing the mean difference in $\dot{V}O_2$ between 15 and 20 min of the CP validation ride (n = 18). The mean difference between time points was 0.00 ± 0.04 L·min^{-1} and was not different from 0 (P = 0.856, d = 0.04). *Circles* represent individual participants. The *square* data point represents the group mean with SD. *Shaded area* shows the upper and lower limits of agreement (+1.96 SD and −1.96 SD, respectively).

corroborated as a reduction in end-tidal, transcutaneous-capillary, or arterial PCO_2. However, after an increase in power output, a delay in the $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ response can be characterized

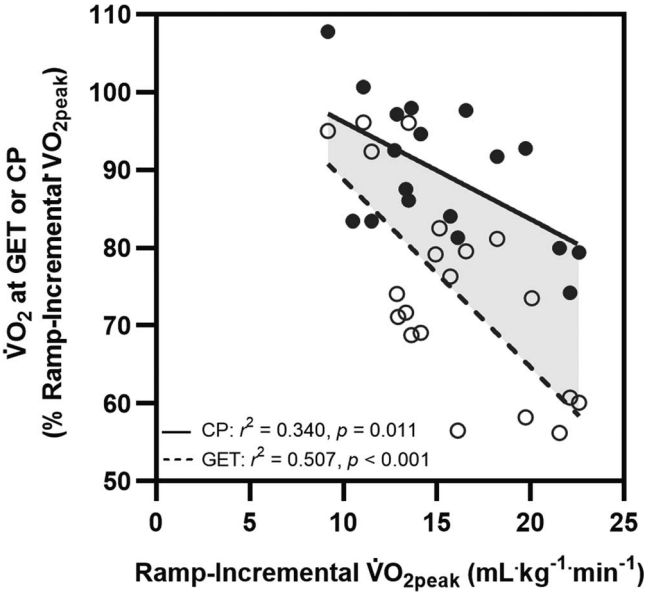


FIGURE 4—The association of $\dot{V}O_2$ at GET with $\dot{V}O_{2peak}$ from ramp-incremental exercise, and $\dot{V}O_2$ at CP with $\dot{V}O_{2peak}$ from ramp-incremental exercise. Relative peak oxygen uptake during ramp-incremental exercise was strongly correlated with $\dot{V}O_2$ at GET (*open circles/dashed line*; r^2 = 0.507, P < 0.001) and modestly correlated with $\dot{V}O_2$ at CP (*closed circles/thick line*; r^2 = 0.340, P = 0.011). Data shown for patients who had an identifiable GET (n = 20) and patients who completed a 20-min ride at CP (n = 18). The difference between GET and CP (i.e., the $\dot{V}O_2$ range of the heavy intensity domain, or "H space") is represented by *gray shading* and decreases congruent with $\dot{V}O_{2peak}$.

via the respective mean response times (42). In healthy subjects, power output becomes dissociated from metabolic processes by a mean response time of ~45–60 s. During incremental exercise with a ramp-rate of 20 $W \cdot min^{-1}$, such a delay is equivalent to 15–20 W. It stands to reason that this dissociation would be exacerbated in patients with chronic diseases that are characterized by slowed $\dot{V}O_2$ kinetics (13). Leo and colleagues (20) were able to mitigate the large differences between power output at CP and RCP by adjusting for the kinetic dissociation, irrespective of the ramp rate (i.e., fast, medium, or slow). Although this is consistent with the finding that $\dot{V}O_2$ at CP and RCP, and the associated power outputs, are closely associated in healthy subjects (19,21), there remains a large root-mean-square error of ~30 W between thresholds, even after adjusting for kinetic effects (13). This suggests that CP and RCP may not be consistently interchangeable.

The third assumption on which an equivalence between CP and RCP depends is that the signaling pathway connecting metabolic acidosis originating in the muscle and respiratory compensation accomplished by the ventilatory system is not unduly influenced by factors external to the organism (such as test protocols or environmental stimuli) or subject pathophysiology. Broxterman and colleagues (16) argued that in order for RCP to be a valid surrogate for CP, the variables should be "consistently and strongly related." Under normal conditions, respiratory compensation attenuates the increase in arterial hydrogen ion concentration $[H^+]$ that is partly responsible for decreasing arterial pH. Keir and colleagues (17) proposed that lactate accumulation at work rates above CP causes a near *immediate* rise in $[H^+]$ and a *rapid, reflexively-driven* compensatory increase in ventilation (i.e., the RCP), concluding that CP and RCP "are surrogates that are linked together by a common metabolic stimulus." However, environmental conditions like hypoxia can sensitize ventilatory control mechanisms such that during ramp-incremental exercise at high altitude, RCP and GET occur simultaneously without an isocapnic buffering region (43). These data speak to the labile nature of RCP.

Pertinently, the equivalence of CP and RCP has so far only been explored in healthy and/or athletic individuals with intact biochemical and respiratory-mechanical signaling. Given that the equivalence between CP and RCP depends on a tightly regulated cascade of physiological mechanisms—progressive muscle acidosis, chemosensory responses to arterial acidosis, and neural-mechanical coupling influencing increased alveolar ventilation—we tested the "equivalence hypothesis" in patients with respiratory-mechanical limitation in whom the physiological cascade is impeded. To our knowledge, this is the first study to do so. The main outcome, that all patients exhibited a valid CP while only three patients produced an identifiable RCP, demonstrates empirically that some pathologies disrupt the sequence of physiological events on which the equivalence of CP and RCP depends.

In COPD, exercise intolerance during ramp-incremental exercise is rarely the result of neuromuscular fatigue (44). Instead, exercise cessation is usually attributable to intolerable dyspnea that results from the complex interplay among expiratory flow limitation, gas trapping, dynamic hyperinflation, and decreasing inspiratory reserve volume congruent with increasing neural respiratory drive (45). Even in mild COPD, the respiratory system may reach its physiological limit at lower peak work rates and ventilations than in healthy populations (46). The low ventilatory reserve in our patients at exercise intolerance (11%–16%) is evidence of a discernable ventilatory limitation. The degree of respiratory-mechanical constraint can also be visualized in some patients as an apparent negative/downward inflection in the $\dot{V}_E$–$\dot{V}CO_2$ relationship toward the end of ramp-incremental exercise (Fig. 3), and this is distinct from the normal positive/upward inflection usually observed in individuals without respiratory-mechanical constraint. As such, although COPD patients exhibit P–T_{lim} profiles that allow the characterization of CP, disease pathophysiology typically denies them the signaling and/or ventilatory mechanics necessary to exhibit respiratory compensation during incremental exercise. Collectively, our data reinforce the contention that CP and RCP are not consistently and strongly related.

CONCLUSIONS

In COPD patients, who present with cardiopulmonary and/or respiratory-mechanical dysfunction, CP and RCP are not equivalent. These data undermine the validity of RCP as a surrogate for CP.

This study utilized data set originally published in 2013/14 (28,29).

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